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Signed Andrew Gregg

Dated 28 October 2004

Patents Form 1/77

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P01/7700 0.00-0324578.4

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

21 OCT 2003

The Patent Office

Cardiff Road
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South Wales
NP10 8QQ

1. Your reference — REP07489GB

2. Patent application number *(The Patent Office will fill this part in)* — 0324578.4

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Arakis Ltd.
Chesterford Research Park
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CB10 1XL

Patents ADP number *(if you know it)* 08306128001

If the applicant is a corporate body, give the country/state of its incorporation — United Kingdom

4. Title of the invention

THE USE OF NON-OPIATES FOR THE POTENTIATION OF OPIATES

5. Name of your agent *(if you have one)*

Gill Jennings & Every

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Broadgate House
7 Eldon Street
London
EC2M 7LH

Patents ADP number *(if you know it)* 745002 ✓

6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months.

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. Divisionals, etc: Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)

Number of earlier UK application	Date of filing *(day / month / year)*

8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request? — YES

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

Otherwise answer NO (See note d)

Patents Form 1/77

9. Accompanying documents: A patent application must include a description of the invention. Not counting duplicates, please enter the number of pages of each item accompanying this form:

Continuation sheets of this form	
Description	6
Claim(s)	1
Abstract	
Drawing(s)	1 + 1

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent (Patents Form 7/77)	
Request for a preliminary examination and search (Patents Form 9/77)	
Request for a substantive examination (Patents Form 10/77)	NO
Any other documents (please specify)	

11. I/We request the grant of a patent on the basis of this application.

For the applicant
Gill Jennings & Every

Signature

Date 21 October 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

R E Perry
020 7377 1377

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Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

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THE USE OF NON-OPIATES FOR THE POTENTIATION OF OPIATES

Field of the Invention

The present invention relates to the use of non-opiates for the potentiation of opiates to boost analgesia.

Background of the Invention

Patients suffering from chronic benign pain and/or cancer pain are often treated with opiates/opioids which are often administered in a controlled release manner. However, from time to time, the analgesic effect cover is insufficient and the patient experiences painful episodes.

Such intermittent, uncontrollable episodes (breakthroughs) are found in chronic benign pain states which can be categorised as musculoskeletal, visceral and headache pain, and include conditions such as osteoarthritis, chronic pancreatitis and chronic migraine. Breakthrough pain is also found in cancer pain conditions associated with the malignant growth of tumours both primary and metastatic in nature. Such conditions are thought to be associated with either pressure on normal tissue (invasion) or the release of pro-nociceptive mediators in and around the tumour.

At present, breakthroughs are treated using rapidly acting supplementary opiates. These are not always seen as desirable, due to problems with illicit diversion and in some cases accidental usage. In addition, they are often administered in such a way as to delay their onset of action, resulting in a shortfall in the analgesia required by the patient.

NMDA NR2B specific antagonists, exemplified by ifenprodil, are known to potentiate opiates (Bernardi et al, 1996). The combination of the side-effects associated with the co-administration of NMDA antagonists and opiates (Hoffman et al, *Pharmacol Biochem Behav*; 2003) produces significantly more respiratory depression, and possibly more emesis and mental clouding, than either agent given alone.

CCK receptor antagonists such as proglumide have been demonstrated to reverse tolerance to opiates, reducing the dose of opiate required to produce analgesia (Kellstein et al, *Pain*; 1991). Consequently, proglumide has been demonstrated to boost opiate analgesia, meaning that a markedly reduced dose

of opioid is required to achieve the same level of analgesia. This has been shown to occur, without any potentiation in respiratory depression (US-A-4576951) or any effect on the development of opiate dependence (Paneria et al., *Brain Research*; 1987).

The pharmacology of proglumide is mixed CCK_A (gastrin) and CCK_B antagonism, its anti-ulceration action being via the inhibition of the CCK_A receptor. Antagonism at the CCK_B receptor has thus far been unexploited and is known to be involved in the development of tolerance to morphine analgesia (Watkins et al, *Science*; 1984). Proglumide when given by the oral route is known to induce headache as its major side-effect.

Noradrenaline/serotonin reuptake inhibitors have been shown to be opiate potentiators (Larsen and Arnt, *Acta Pharmacol Toxicol*; 1984). They are exemplified by desipramine, a classical antidepressant, and nefopam which is a non-opiate analgesic drug. Such compounds have a number of side-effects at oral therapeutic doses, which include cardiovascular abnormalities, restlessness, insomnia, ataxia, dry mouth and emesis.

Adrenergic stimulating agents include agents which stimulate $alpha_2$ adrenoceptors and potentiate opiates. Alpha adrenoceptor agonists are exemplified by clonidine. Clonidine is a strong non-opiate analgesic which is often given intrathecally at analgesic doses to avoid its poor side-effect profile which includes hypotension, emesis, weight gain, nervousness and fatigue. Beta adrenoceptor agonists are exemplified by salbutamol. Salbutamol is a bronchodilator which is given via the pulmonary route by dry powder inhaler. Its side-effects are typical of the beta adrenoceptor agonists, i.e. tremor, tachycardia, tension, headaches and peripheral vasodilation.

COX inhibitors are generally known to potentiate the effects of opiates and are often used in combination with weak opiates for the treatment of moderate pain (cocodamol and coproxamol). Diclofenac is an example of a mixed COX inhibitor. Therapeutic doses of diclofenac have side-effects include gastric ulceration, abdominal cramps, constipation and dizziness.

Summary of the Invention

The present invention is a new use for non-opiate analgesics for the potentiation of opiates in the treatment of breakthrough pain associated with chronic benign pain or cancer pain states. The dose of non-opiate can be low enough not to induce side-effects often associated with either the non-opiate alone or the combination of non-opiate and opiate.

In particular, it has been found that intranasal use of non-opiate, opiate potentiators allows lower doses of the potentiators than those used for oral administration. This has the advantage of minimising the side-effects commonly attributed to the drugs in question.

As breakthrough pain requires immediate relief, clinicians and patients alike would find it desirable to administer a dose of the non-opiate potentiator of opiates through the nasal delivery route. Potentiation via this route is rapid, and follows a time course similar to that seen with intravenous administration and can provide an improved treatment over those currently available. In addition, this route avoids first-pass metabolism, but also allows quicker penetration to the CNS, which may allow the administration of lower doses than are needed for other indications. This reduces the side-effects of the non-opiate.

Description of the Invention

This invention involves the use of non-opiates (which may be described herein as potentiators). They are used in treatment where an opiate such as morphine, and of which many other examples are known to those skilled in the art, is being used.

Non-opiates suitable for use in the present invention include NMDA antagonists specific for the NR2B subunit. These are exemplified by ifenprodil, felbamate and eliprodil.

Suitable non-opiates also include CCK antagonists. These are exemplified by proglumide, devazipide and loxiglumide.

Further suitable non-opiates include biogenic amine reuptake inhibitors (antidepressants, neuroleptics and analgesics), which inhibit reuptake of noradrenaline and serotonin. Antidepressants include agents such as adrafinil, amfebutamone, amitriptyline, amitriptylinoxide, amixetrine, amoxapine,

benmoxin, binedaline, butriptyline, caroxazone, carpipramine, citalopram, clomipramine, desipramine, dibenzapine, dimetacrine, dosulapine, doxepine, etoperidone, fenpentadiol, fipexide, fluoxetine, fluvoxamine, imipramine, indalpine, indeloxacine, iproniazid, isocaroxazid, lofepramine, maprotiline, medifoxamine, melitracen, metapramine, mianserin, milnacipran, minaprine, mirtazapine, moclobemide, nefazodone, nialamide, nomifensine, nortriptyline, noxiptiline, opipramol, oxaflozane, paroxetine, phenelzine, protirelin, protriptyine, quinupramine, reboxetine, sertraline, setiptiline, sibutramine, sulpiride, sultopride, tandospirone, tofenacin, toloxatone, tranylcypromine, trazodone, trimipramine, venlafaxine, viloxazine and zimeladine. Analgesic reuptake inhibitors include agents such as tramadol, duloxetine, nefopam and venlafaxine. Neuroleptics include agents such as acepromazine, aceprometazine, acepromazine, aceprometazine, acetophenazine, alizapride, benactyzine, benperidol, bromperidol, butaperazine, clopenthixol, chlorpromazine, chlorprothixene, carfenazine, clozapine, cyamemazine, deserpidine, dixyrazine, droperidol, fluanisone, flupentixol, fluphenazine, fluspirilene, haloperidol, homofenazine, levomepromazine, loxapine, mosapramine, moperone, melperone, oxypertine, pipamperone, pimozide, perphenazine, perimetazine, periciazine, penfluridol, pecazine, pipotiazine, piperacetazine, prothipendyl, promazine, profenamine, sulforidazine, spiperone, timiperone, tiapride, thioridazine, thioproperazine, thiopropazate, tiotixene, trifluoperazine, trifluperidol, triflupromazine and zotepine.

Non-opiate potentiators of opiates also include agents which potentiate the noradrenergic system by acting as $beta_2$ adrenoceptor agonists. Agents which stimulate $beta_2$ adrenoceptors include drugs such as albuterol, bambuterol, bitolterol, broxaterol, carbuterol, clenbuterol, eformoterol, fenoterol, folmoterol, foradil, isoproterenol, metaproterenol, pirbuterol, procaterol, salbutamol, salmeterol, reproterol, rimiterol, terbutaline, tretoquinol and tulobuterol.

Non-opiate potentiators of opiates also include agents which potentiate the noradrenergic system by acting as $alpha_2$ adrenoceptors agonists. Agents

which stimulate alpha2 adrenoceptors include drugs such as brimonidine, clonidine, medetomidine, moxonidine, rilmenidine and tizanidine.

Non-opiate potentiators of opiates also include cyclooxygenase (COX) inhibitors, which include non-selective COX inhibitors, selective COX-2 inhibitors such as celecoxib, selective COX-3 inhibitors such as paracetamol, COX inhibitors linked to NO donors and dual action COX and lipoxygenase (LOX) inhibitors. The use of these compounds can be free of GI side-effects commonly associated with these agents delivered orally.

COX inhibitors are exemplified by agents such as aceclofenac, acemetacin, alcofenac, alminoprofen, aloxipirin, amfenac, aminophenazone, antraphenine, aspirin, azapropazone, benorilate, benoxaprofen, benzydamine, butibufen, chlorthenoxacine, choline salicylate, chlometacin, dexketoprofen, diclofenac, diflunisal, emorfazone, epirizole, etodolac, feclobuzone, felbinac, fenbufen, fenclofenac, flurbiprofen, glafenine, hydroxylethyl salicylate, ibuprofen, indometacin, indoprofen, ketoprofen, ketorolac, lactyl phenetidin, loxoprofen, mefenamic acid, metamizole, mofebutazone, mofezolac, nabumetone, naproxen, nifenazone, oxametacin, phenacetin, pipebuzone, pranoprofen, propyphenazone, proquazone, salicylamide, salsalate, sulindac, suprofen, tiaramide, tinoridine, tolfenamic acid and zomepirac.

Selective COX-2 inhibitors are exemplified by agents such as celecoxib, etoricoxib, lumiracoxib, meloxicam, parecoxib, rofecoxib, tilmacoxib and valdecoxib. Selective COX-3 inhibitors are exemplified by agents such as antipyrine, dipyrone, paracetamol and phenacetin. COX inhibitors linked to NO donors are exemplified by agents such as nitroflurbiprofen, nitronaproxen and nitrofenac. Dual action COX and lipoxygenase (LOX) inhibitors are exemplified by agents such as licofelone and ketoprofen.

A compound for use in the invention may be in any suitable form, e.g. as a salt. Further, if the compound is chiral, any enantiomeric form, or a racemic or non-racemic mixture, may be used.

A preferred non-opiate for use in the present invention is ifenprodil. It has been found that intranasal dosing is the ideal route of administration of ifenprodil for the potentiation of opiates. An intranasal formulation of ifenprodil is

described in PCT/GB03/01906 and in another British Patent Application, having the same date as this, entitled "The Treatment of Pain".

Another preferred agent is nefopam; see PCT/GB03/02618 for general information and an example.

The following Example illustrates the invention.

Example

In this Example, the potentiation of opiate analgesia has been demonstrated, by a nasally administered non-opiate agent, in the rat tail flick assay. Figure 1 shows the results, and the significant potentiation of morphine analgesia with a non-analgesic dose of the non-opiate agent.

In Fig. 1, results are expressed as mean ± sem for 6 experiments, which are (from left to right): vehicle, morphine (6 mg/kg), vehicle, ifenprodil (1 mg/rat), vehicle IN + vehicle IP, and ifenprodil IN (1 mg/rat) + morphine IP (6 mg/kg).

vehicle: 90% saline 10% propylene glycol

vehicle and morphine were intraperitoneally given 30' before the test

vehicle and ifenprodil were intranasally given 30' before the test

n= 10 rats per group

student's T test: * indicates a significant difference in comparison to the vehicle group for $P<0.05$

student's T test: † indicates a significant difference in comparison to the morphine group for $P<0.05$

These results indicate that ifenprodil can be used in the treatment of breakthrough pain. In particular, the data show that ifenprodil potentiates morphine when administered intranasally and therefore has the ideal characteristics to be used in the treatment of breakthrough pain (low pain, rapid onset, low or no side-effects).

CLAIMS

1. Use of a non-opioid analgesic for the manufacture of a medicament for the treatment of intermittent or episodic pain experienced by a patient undergoing chronic pain treatment with an opioid analgesic.

2. Use according to claim 1, when the pain is chronic benign pain.

3. Use according to claim 2, where the pain is related to a musculoskeletal, visceral or headache condition.

4. Use according to claim 3, where the condition is osteoarthritis, chronic pancreatitis or chronic migraine.

5. Use according to claim 1, when the pain is breakthrough pain in cancer.

6. Use according to any preceding claim wherein the non-opioid analgesic is an antagonist of NMDA, CCK, substance P or neurokinin, causes uptake blockade, is an agonist of $alpha_2$ or $beta_2$ adrenoceptors or is a COX inhibitor.

7. Use according to any preceding claim, wherein the non-opioid analgesic is clenbuterol, proglumide, devazepide, ifenprodil, nefopam, tramadol, duloxetine or venlafaxine.

8. Use according to any preceding claim, wherein the medicament is for administration via a route that avoids first-pass metabolism.

9. Use according to claim 8, wherein the route is intranasal.

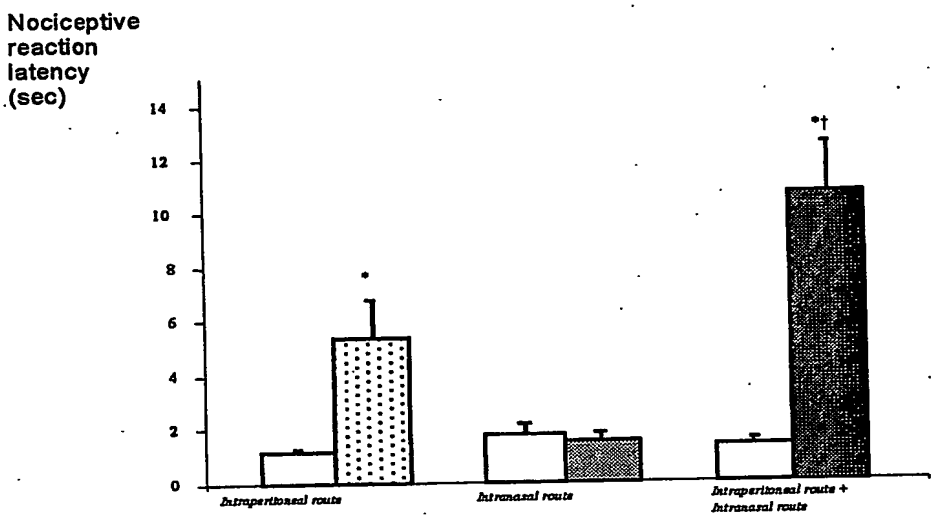
Nociceptive reaction latency (sec)
14
12
10
8
6
4
2
0
*
*†
Intraperitoneal route
Intranasal route
Intraperitoneal route + Intranasal route

Fig. 1